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Original Article

Immunopathogenesis of acute on chronic liver failure

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ABSTRACT

Acute-on-chronic liver failure is a well-established description of a high-mortality syndrome of chronic liver disease (usually cirrhosis) with organ failure. While the exact definition is under refinement, the accepted understanding of this entity is in patients with chronic liver disease and various organs in failure and where systemic inflammation is a major component of the pathobiology. There are limited therapies for a disease with such a poor prognosis, and while improvements in the critical care management and for very few patients, liver transplantation, mean 50% can survive to hospital discharge, rapid application of new therapies is required. Here we explain the current understanding of the immunologic abnormalities seen in acute-on-chronic liver failure across the innate and adaptive immune systems, the role of the hepatic cell death and the gut-liver axis, and recommendations for future research and treatment paradigms.

1. Introduction

The syndrome of acute-on-chronic liver failure (ACLF) occurs in patients with chronic liver disease in the context of acute decompensation (AD) of liver function together with 1 or more extrahepatic organ failures. It is associated with a high short-term mortality rate[1,2] and occurs in 30% of patients hospitalized for AD.[1] According to the European Association for the Study of the Liver (EASL) definition, ACLF is classified into 3 grades based on the number of organ failures, with higher grades associated with increasing risk of 28-day mortality, varying from 23% to 77% in grades 1 to 3, respectively.[1] Other international societies have not mandated that patients must have cirrhosis in their definition, and the definition for organ failure also varies. The EASL definition does not require the presence of hyperbilirubinemia or coagulopathy in contrast to the World Gastroenterology Society or the Asia Pacific Association for the Study of the Liver. Thus, the presence of portal hypertension or a classical description of liver failure is not universally part of the global understanding of ACLF. Nevertheless, some common clinical components do permeate all definitions including precipitating events, clinical phenotypes, and the inflammatory response.

The development of ACLF is often precipitated by bacterial infection, gastrointestinal hemorrhage, alcohol-related hepatitis (AH), relapsed chronic viral hepatitis and surgery.[1,2] Treatment is largely based on managing precipitating events and associated

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complications and providing organ support.[2-4] However, these approaches are often ineffective, especially in severe cases where mortality exceeds 50%. Liver transplantation is the only curative treatment for ACLF, and there is a clear survival benefit in highly selected patient groups.[5,6] Moreover, these patients show acceptable outcomes at 1 year with survival >80% even in the most severely ill.[6-8] Although many patients with ACLF are at present unlikely to meet the present stringent criteria for ACLF-transplant listing, ongoing advancements are likely to increase the potential recipient pool in the years ahead. The opportunities to enhance organ preservation via perfusion devices and ongoing studies into allocation and prioritization for waitlisted patients with ACLF mean this is a rapidly expanding area of transplantation. To prevent organ shortage by a large expansion of the ACLF recipient pool, it is also necessary to develop new approaches to optimize the transplant-free survival of patients with ACLF before widespread changes in practice.

ACLF is a dynamic syndrome with deterioration, improvement, or resolution in hours to days. This may be related to the immunopathology and immunoplasticity of the circulating and hepatic environments. A central paradox is the proinflammatory state (evidenced by high systemic cytokine release) together with a relative state of immune suppression (prorestoration innate immune phenotypes with high rates of sepsis). There is growing high-quality evidence demonstrating the key role played by systemic inflammation and immune dysfunction in the development of ACLF, which provides both the rationale for developing immune-based therapeutic strategies and implies that their application will be complex. This approach is attractive because modulation of immune system function has recently been associated with improved outcomes in cancer, inflammatory diseases, or sepsis (including COVID-19). Immunomodulatory therapies, such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, have revolutionized the treatment of certain cancers.[9-12] Sphingosine 1-phosphate receptor modulators, which modulate lymphocyte function, reduce relapse rate in multiple sclerosis, and show promise in the treatment of inflammatory bowel diseases.[13]

Therefore, this review will focus on the immunopathogenesis of ACLF (Figure 1) to inform the reader of the most up-to-date concepts and contextualize emerging immunomodulatory strategies.

2. Initial hepatic insults and the hepatic microenvironment in ACLF

In patients without cirrhosis, acute liver failure (ALF) is associated with an initial hepatic insult, variable intrahepatic necrosis, followed by immune activation. It was thought previously that ACLF had less hepatic cell death but, while distinct to ALF, it is now appreciated that hepatocyte cell death plays a major role in the development of ACLF. Damage-associated molecular patterns (DAMPs; such as high-mobility group box 1 protein and histones) are released from injured, dying or dead cells. DAMPs are increased in ACLF because immunogenic forms of cell death such as necrosis, necroptosis, and pyroptosis, become predominant.[14] Pathogen-associated molecular patterns (PAMPs), highly conserved essential bacterial molecules, such as lipopolysaccharide (LPS), are also increased due to infections and enhanced gut bacterial translocation. Intrahepatically, DAMPs and PAMPs are recognized by pattern recognition receptors including Toll-like receptors (TLRs, eg, LPS is recognized by TLR4).[15] TLR4 is expressed by multiple cell types, including monocytes, Kupffer cells, and hepatocytes. Upregulated hepatic TLR4 expression may sensitize the liver to LPS-driven tissue injury.[16-19] LPS binding to TLR4 induces proinflammatory cytokine secretion, triggering further inflammation, cell death, and liver injury. The production of proinflammatory cytokines requires inflammasome activation (an intracellular multiprotein complex that converts procaspase 1 to activated caspase 1), which then

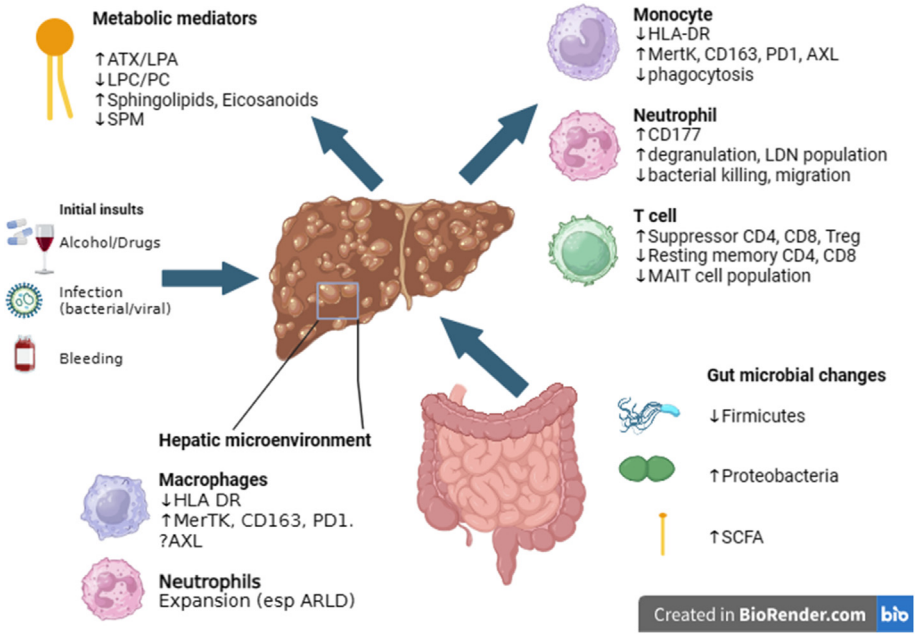

Figure 1. Immunopathology of acute-on-chronic liver failure. The cirrhotic liver is destabilized by insults such as drugs, alcohol, viruses or from bleeding and infection. Intrahepatic immune processes initially involve activation of macrophages and neutrophils with the hepatic pool expanding rapidly in alcoholic hepatitis. Peripheral neutrophil over express CD177 and degranulate inappropriately and show deficient ROS production. Macrophages and peripheral monocytes move from proinflammatory to compensatory inflammatory phenotypes expressing MerTK, CD163, and PD1. This is associated with reduced phagocytic capacity. T cells exhibit changes that are also measurable in the early phases of compensated and decompensated cirrhosis and underlie cirrhosis-associated immune dysfunction (CAID). Gut microbial diversity reduces and dominant proteobacteria and reduced firmicutes (among many other changes) are associated with high short-chain fatty acid production (SCFA) and fecal cytokine disturbance. Metabolic abnormalities include reduced phosphocholine (PC) and lysophosphatidylcholine (LPC) under the action of autotaxin (ATX), thus increasing circulating lysophosphatidic acid (LPA). Sphingolipid and leukotriene increases are also seen, and these metabolic changes can perturb circulating immune cells.

converts pro–interleukin (pro-IL)-1β to bioactive IL-1β.[20] IL-1β contributes to chemokine production that results in the recruitment of neutrophils and monocytes to the liver and activation of Kupffer cells.[21] IL-1α is produced in response to a noncanonical activation of the inflammasome. These cytokines in ACLF are important as single nucleotide polymorphisms in the IL-1β and IL-1 receptor antagonist (IL-1ra) genes, resulting in reduced levels of circulating IL-1β and IL-1α, are protective against ACLF.[22] Additionally, circulating levels of IL-1α predict development of fatal ACLF in compensated cirrhosis, whereas circulating levels of IL-1β predict ACLF development from AD.[23]

As noted earlier, cytokine release in ACLF appears bimodal and excessive in the early stages of disease although there is the opposite seen in the ex vivo setting where monocytes are hyporesponsive to bacterial cues. Further complexity is seen when the differing forms of IL-1α and 1β are explored. IL-1α is released by dying (epithelial) cells, whereas IL-1β is a product of inflammasomes in tissue at sites if inflammation (both sterile and infected). Hence, IL-1β is myeloid derived and IL-1α by a wider set of cell types. ELISAs do not always capture the concentration of these cytokines owing to either their cellular origin or whether they have been processed within or outside inflammasomes.[24]

Intrahepatic neutrophil migration is responsible for hepatocyte cell death.[25] The chemokine receptors, CXCR1 and CXCR2, expressed on neutrophils, are required for chemotaxis to sites of liver injury.[26] Higher neutrophil expression of CXCR1 and CXCR2 in ACLF may contribute to hepatocyte cell death and inflammatory cytokine production.[25] Monocyte infiltration intrahepatically may perpetuate injury and secretion of proinflammatory cytokines, whereas in situ development to macrophages promotes resolution of tissue injury.[27] In hepatitis B virus (HBV)-related ACLF, increased intrahepatic natural killer (NK) cells contributes to hepatocyte cell death, partly through pathways involving various NK-cell surface receptors.[28-30] There is emerging evidence of a link between the NLRP3 inflammasome in both HBV and hepatitis C virus (HCV) albeit not always in the context of ACLF. However, in murine models of HBV infection, HBeAg can inhibit LPS-induced NLRP3 inflammasome activation, and in HCV, NLRP3 expression is increased in both hepatocytes and macrophages.[31] Functionally, IL-18 secretion in the wake of NLRP3 activation stimulates NK cells to secrete interferon. While this can help in the control of HCV, the DAMPs from pyroptotic cells can still lead to secondary sterile inflammation and liver injury.

Underlining the importance of the adaptive immune response in viral causes of cirrhosis and ACLF is the recent observation that the cytotoxic T-lymphocyte liver damage associated with viral hepatitis appears to also occur in ACLF. Enlarged hepatic populations of $CD4^+$ and CD8 T cells are associated with hepatic necrosis in HBV-related ACLF[32] and is worsened by reduced regulation via PD-1.[33]

Finally, while regeneration is crucial for recovery of liver function after injury, it appears impaired in ACLF, especially AH.[34,35] Hepatocyte proliferation capabilities are markedly reduced, which is thought to be a result of different causes involving decreased levels of growth factors produced by liver endothelial cells and liver mesenchymal stem cells together with an increased transdifferentiation of hepatocytes to biliary cells.[35,36]

Interestingly, mechanisms involved in liver damage and systemic inflammation differ according to the etiology and triggering events of ACLF. Bacterial infection–induced ACLF leads to increases in tumor necrosis factor (TNF)-α, IL-6, and IL-1ra, whereas alcohol-induced ACLF leads to a significant increase in IL-8.[37] Bacterial infections induce inflammation through recognition by dedicated pattern recognition receptors and through virulence factors resulting in high levels of TNF-α, IL-6, and acute-phase response proteins.[38] In contrast, excessive alcohol consumption results in gut bacterial dysbiosis and increased intestinal permeability.[39] In nonalcoholic steatohepatitis, hepatic immune cells are activated by inflammatory mediators from adipose tissue and the gut.[40] Infections trigger both innate and adaptive immunity, whereas DAMPs predominantly induce innate inflammation.[41] An ex vivo study found that neutrophil dysfunction in HBV-related ACLF was influenced by the circulating environment, and therefore, different circulating cytokine profiles in the various precipitating events of ACLF could have different impacts on immune cells.[42] Furthermore, patients with alcohol-related cirrhosis and active alcoholism who develop ACLF are younger, have more pronounced derangements in laboratory tests (leukocyte count, aspartate aminotransferase and bilirubin) and develop more severe ACLF than those without active alcohol use.[1,43]

3. Systemic inflammation and immune dysfunction in ACLF

Systemic inflammation is a key driver in the development of ACLF[18,44-47] and progresses in severity from compensated states to ACLF.[45,46] This intense systemic inflammation is characterized by a large increase in plasma levels of proinflammatory cytokines (IL-6 and TNF-α), chemokines, adhesion molecules, soluble markers of macrophage activation (soluble cluster of differentiation 163, and mannose receptor), C-reactive protein, and circulating white blood cells.[1,37,46,48] Notably, the severity of the systemic inflammation correlates with the degree of organ failure and survival.[37,46] Immunometabolism also plays an important role with major changes including enhanced glycolysis and decreased mitochondrial β-oxidation.[49] The resulting decrease in fatty acid–based energy supply, combined with the mitochondrial reactive oxygen species (ROS) induced by inflammation, contribute to mitochondrial dysfunction and metabolic suppression in peripheral organs.[49,50]

Alongside this intense systemic inflammation, there coexists an excessive compensatory anti-inflammatory response, with functional defects of circulating immune cells and an increase in mediators with anti-inflammatory potential such as IL-10, IL-1ra, and prostaglandin E2,[18,37,45,47,51] patients prone to developing frequent bacterial infections associated with high mortality.[52]

3.1. Neutrophils

Neutrophils have long been associated with dysfunctional immunity in ACLF. Classically, there is an increased neutrophil

count and an elevated neutrophil-to-lymphocyte ratio, which predicts mortality,[25,53] potentially related to emergency granulopoiesis with exaggerated granulocyte colony-stimulating factor (G-CSF) levels.[54,55] Transitioning from fibrosis to cirrhosis to ACLF, circulating neutrophils exhibit impaired functional capacities in migration and bacterial killing (eg, phagocytosis, degranulation, ROS production and neutrophils extracellular trap [NET] formations).[56-58] Alongside these functional defects, circulating neutrophils are phenotypically primed showing an exacerbated resting activation leading to energy depletion and associated with an exhausted phenotype impairing bacterial defense.[54,58,59] Bulk transcriptomics have demonstrated that markers of degranulation are upregulated in ACLF and inappropriate CD177 overexpression (mediating firm adhesion to endothelial cells), causing ineffective degranulation, potentially far from the site of injury or infection leading to tissue damage including the liver and release of further DAMPs.[25,60] Recent data have suggested that NETs take part in AH, one of the leading causes of ACLF, and that macrophages in AH have impaired efferocytosis function regarding NETs-producing neutrophils.[60] A decrease in migration capacity of circulating neutrophils toward IL-8 and leukotriene B4[61,62] and alteration of neutrophils' migration capacities are considered to play a role in heightened tissue inflammation and reduction in bacterial killing capacities in ACLF.

A subpopulation of neutrophils with decreased density, called low-density neutrophils (LDNs), is increased in patients with AH.[55,60] Unexpectedly, AH-LDNs exhibited a mature neutrophil phenotype. Evidence suggests that AH-LDNs are generated from high-density neutrophils, the main neutrophil subpopulation, after NET release. Transcriptional phenotyping and functional assays of AH-LDNs show an exhausted phenotype with reduced phagocytic capacity and decreased ROS production at baseline and on stimulation. As LDNs trends to persist in the blood due to reduced homing capacities, this subpopulation is potentially critical in the alteration of neutrophils functions observed in AH.[60]

Therefore, utilizing therapies to improve neutrophils' function could potentially reduce susceptibility of infection. In patients with decompensated cirrhosis, the deficient degranulation, ROS production and bacterial killing by neutrophils from patients with cirrhosis can be rapidly corrected in vitro with TLR7/8 agonists stimulating NOX2 synthesis via an mTOR-dependent mechanism.[56,63] G-CSF–based strategy can also improve neutrophils count and capacity although potentially harmful in liver damages.[64-66] Hence, G-CSF should not be used alone, and animal studies have shown that a combination of G-CSF and a TLR4 inhibitor may limit inflammation, cell death, and hepatocyte proliferation.[66,67]

3.2. Monocyte/macrophages

One of the first demonstrated defects in monocyte biology in ACLF was reduced expression of HLA-DR, subsequently impairing antigen presentation.[68] Together with expanded immunosuppressive monocytic populations, predominantly expressing MER receptor tyrosine kinase (MERTK+), programmed death ligand 1 (PD-L1+), anexelekto (AXL+), with expanded monocytic myeloid-derived suppressor cells.[68-70] As an example, when monocytes are reprogammed from HLA-DR^{high}/MerTK^{low} to HLA-DR^{low}/MerTK^{high} TLR-elicited inflammatory responses to microbial challenge are reduced and impaired T-cell function ensues.[68] In addition, reduced expression of TLR2 and TLR4 and reduced phagocytic capacity occur in classical CD14^{++}CD16^{-} monocytes of patients with ACLF. Such immune-suppressive phenotypes are associated with upregulated expression of CD163, IL-10, and MERTK. Illustrating the interplay between immune phenotype and metabolism, metabolic rewiring of the cells using a pharmacologic inhibitor of glutamine synthetase, partially restores phagocytic and inflammatory capacity of in vitro generated and ACLF patient-derived monocytes.[71] Information on tissue resident macrophages is limited in ACLF, although expansion of hepatic macrophages expressing high levels of MERTK and CD163 in patients with ACLF undergoing liver transplantation has been reported.[69,71]

3.3. Lymphocytes and the adaptive response

Recent studies indicate an early occurrence of dysregulation of adaptive immune system participating in the pathogenesis of ACLF.[72] Although lymphopenia is a common feature of patients with ACLF, whole-blood RNA microarray analyses identified a downregulation of RNA signatures of resting memory CD4 T cells, CD8 T cells, and memory B cells.[57] Besides its reduction in the circulation in ACLF, an accompanied immune-suppressive phenotype of lymphocytes occurs.[72] Peripheral suppressor CD8^{+} T cells, characterized by high HLA-DR and T-cell immunoglobulin and mucin domain-containing protein 3 expression, are expanded in patients with cirrhosis and their circulating level correlates with infection and disease severity.[73] Although classical regulatory T cells are expanded in patients with AD and ACLF, the presence of a cytokine-driven immunosuppressive CD4^{+} circulatory T-cell population has been reported in patients with AD.[72,74] Transcriptomic analyses excluded the possibility that these were classical thymic-derived regulatory T cells (Tregs). This population, identified by the expression of HLA-G (a nonclassical HLA class I molecule), cytotoxic T lymphocyte–associated protein 4 and IL-35 (an anti-inflammatory cytokine), has been associated with increasing disease severity, bacterial infections, and poor outcome in patients with AD.[74] The CD4 subgroup is formed in the periphery and exerts suppressive properties via CTLA-4 and HLA-G–driven inhibition of T_H17-related cytokines. IL-35 levels increased after the challenge of Kupffer cells by PAMPs and induced an expansion of regulatory T cells, illustrating the elaborate ties between innate and adaptive immune systems.[54] In patients with AH, T cells have increased expression of negative regulatory receptors including programmed cell death protein-1 and TIM3.[75] A significant reduction in both blood and liver naïve B cells in patients with ACLF has been described combined with an increase in antigen-experienced B cells in the liver. In addition, significant phenotype changes within the B-cell compartment have been reported. For instance, atypical CD27^{-}CD21^{-} memory B cells, also known as inflammatory or age-associated B cells, were increased in the periphery and in the liver of patients with ACLF, where they expressed higher levels of CD11c and CXCR5 than that by cirrhotic patients without ACLF,

suggesting once again chronic and persistent antigen stimulation.[54,76,77] Further mechanistic understanding of the lymphocyte compartment and its impact on the natural course of the disease could lead to novel therapeutic target in the future.

4. The gut-liver axis

It is impossible to discuss inflammation in ACLF without consideration of an important source of inflammatory cues and controls in the gut. Other than the gut microbial community that can be perturbed pathologically, a host of immunometabolic mediators and cellular responses in the intestinal wall generate important pathologic sequelae before the liver is involved.

This systemic inflammation can be initiated by PAMPs from bacterial infections or from intestinal translocation of bacterial components. Second infections independently increase mortality in hospitalized patients with cirrhosis: dysbiosis causes intestinal inflammation, which leads to increased pathologic gut bacterial translocation and, therefore, contributes to systemic inflammation.[78] Specific phyla such as proteobacteria are associated with poor outcomes and progression in ACLF.[79] Both increased proteobacteria and reduced firmicutes are associated with changes in inflammatory mediators partly because of their association with endotoxin production,[80] although more detailed mechanisms have not yet been elucidated.

Recent novel findings corroborate a long held clinical suspicion that the predisposition to fungal infection in acute-decompensated and ACLF may be driven by gut microbial changes. Fungal dysbiosis is present in patients with alcoholic hepatitis[81] and contributes to mortality. Exotoxins such as candidalysin and citolysin are hepatotoxic and are detectable and increase the risk of death.[82] In a similar expansion of microbial knowledge pathogenic changes in the intestinal virome have been reported in alcoholic hepatitis.[83] These findings require corroboration in patients with ACLF of non-alcohol etiologies.

Notably, the fecal cytokine pool is uniquely perturbed and intense investigation into the cellular and microbial causes of this are ongoing. Additionally, microbial metabolites correlate with the development of ACLF, especially short-chain fatty acids, and distinct microbiome profiles have been found in the stool and blood of patients with ACLF.[80,84-86] The immunologic response to dysbiosis remains inadequately described but is likely to implicate MAIT cells and the dominant intrahepatic T-cell. These unconventional T cells sit at the border of innate immunity and respond both secondary to and independently of the conventional T-cell receptor via various cytokine receptors. Intrahepatic MAIT cells respond with a flood of cytokines often in response to gut bacterial metabolite cues or hepatic cytokine expression.[87] The level of evidence for a mechanistic or prognostic role is presently sparse, but small studies have shown that an inability to expand the peripheral MAIT cell compartment to be associated with lower survival in ACLF.[88]

5. Immunometabolism

Enormous metabolic changes occur in ACLF. Several metabonomics studies have demonstrated differences in carbohydrate, lipid, amino acid, and bioenergetics intermediate metabolism.[49,89] To some extent, these occur during the progression through decompensation of cirrhosis, but ACLF is a metabolic end point. Metabolomics approaches have indicated a preferential cellular use of glucose (cytosolic aerobic glycolysis and pentose phosphate pathway) for anabolism rather than a mitochondrial use for ATP production. Mitochondrial dysfunction appears also to govern the immunometabolism of circulating leukocytes.[90] Nonessential amino acids and 1-carbon metabolism network are also involved in anabolism of proteins, nucleotides, and lipids to support leukocytes proliferation.[49,59] In these patients, a low dietary intake is common (partly related to an inflammation-induced anorexia). Nutrients are, therefore, issued from liver glycogenolysis and skeletal muscle proteolysis and reallocated to support the high metabolic demand of the activated innate immune compartment at the expense of peripheral organs.[54] Potentially, peripheral organs adapt and shift toward a "dormancy program," leading to hypometabolism characterized by a decreased mitochondrial respiration and ATP production. This mechanism associated with a decreased effective arterial blood volume could participate in peripheral organ failure.

Clinically, hyperammonemia and hyponatremia are common in ACLF although their importance to outcome and inflammation somewhat disputed. In animal models of cirrhosis, ammonia induces neutrophil swelling with reduction in phagocytic capacity (mediated through the p38 [MAPK] pathway). In the in vitro setting, ammonia causes dendritic cell phagocytic dysfunction via mitochondrial damage.[91,92] Similarly, hyponatremia, as well as contributing with ammonia to induce at least some form of cerebral edema, is associated with higher risks of infection.

Lipids are organic compounds derived from fatty acids that are insoluble in water. Although seen primarily as an energy substrate, they are also pivotal inflammatory and anti-inflammatory molecules crossing the boundary of metabolism and the immune system. They have been investigated in multiple inflammatory conditions and, more recently, in ACLF. At least 3 main families of bioactive lipid mediators are known, derived mainly from structural polyunsaturated fatty acids. They are eicosanoids (mostly proinflammatory and deriving from ω-6 fatty acids), specialized proresolving mediators (mostly prorestorative and deriving from ω-4 fatty acids) and lysophospholipids (immunoregulatory and comprising lysoglycerophospholipids and lysosphingolipids). While in ACLF an eicosanoids storm is probable, deficits also occur in proresolving lipid mediator both in plasma and in extracellular vesicles.[93,94]

Interestingly, phospholipids are emerging as an important potential biomarker of outcome. Of mechanistic relevance is the crosstalk between immune and metabolic dysfunction where, in tandem to a growing understanding of immunometabolism,

generally, ACLF could be an exemplar of metabolic control of immunological processes.

We recently demonstrated that the perturbation of the lysophosphotidylcholine-autotaxin-lysophosphatitdic acid axis is upregulated[95] (due to increased ATX expression in hepatocytes), leading to LPA-induced monocyte activation with reduced MerTK and CD163 expression. LPA also modulates cytokine expression by $CD14^{+}$ monocytes via LPA receptors but the exact pathway remains to be described. Interestingly this pathway appears similarly perturbed in ALF.[96]

Bile acid (BA) retention is a feature of AD/ACLF even when the underlying etiology of cirrhosis is not cholestasis related. BAs are steroids synthesized in the liver, secreted in bile, and undergo conjugation in the gut. They not only are emulsifiers used in digestion but also possess potent immune signaling properties. Gut microbiome changes in cirrhosis may therefore impact and be modulated by bile acids and the complex interplay between these molecules and microbes is of considerable interest in the immunometabolism of ACLF. BA can decrease monocyte cytokine production through the TGR5 receptor[97]and further evidence of direct actions of BA on immune function will help guide future therapeutic strategies.

6. Clinical sequelae and the role of transplantation

As our understanding of the immune environment of ACLF grows, so does our appreciation of the difficulties of treating this high-mortality syndrome and how transplantation fits into treatment paradigms. Because extrahepatic organ failure is a well-recognized feature, clinicians are often faced with difficult decisions on how to treat and to decide if transplant is feasible or too high risk.

While attempts have been made to rationalize a global definition of ACLF the extrahepatic organ failures inherent and vital to its definition have heterogeneous pathologic mechanisms (Figure 2). Nitrous oxide–mediated vasoplegia along with diastolic cardiac dysfunction can present in tandem with hyperammonemia and low-grade cerebral edema with or without prerenal azotemia and hepatorenal syndrome. While the hematological issues of myeloid and lymphoid lineages underlie the immunobiology, we described that there are still many unanswered questions on the optimum therapies. G-CSF monotherapy has failed, and combinations with TLR9 modulation may yield better results, but, although we await a more cohesive definition, it is likely that trials in AH with ACLF will lead the way.

Transplantation remains the only curative option (Figure 3), and intense efforts are ongoing to understand which patients benefit (likely to be many) and which patients represent an excess risk. Immunopathology can cross the transplant procedure, but our understanding of the inflammatory environment of patients with posttransplant ACLF is in its infancy compared with that of the nontransplanted patient. The role of adaptive immunity under the influence of immunosuppression is likely to take a more central role, and which biomarkers (such as procalcitonin or cytokines) can help clinicians in the detection of excess infection-driven inflammation will be an area of focus.

7. Conclusion

Our present understanding of the immunopathogenesis of ACLF has improved greatly in the last decade (Figure 1). Despite our new knowledge, no immune relevant therapies have met with success in clinical trials, and mortality remains elusively high in these patients. Future directions should be targeted in several

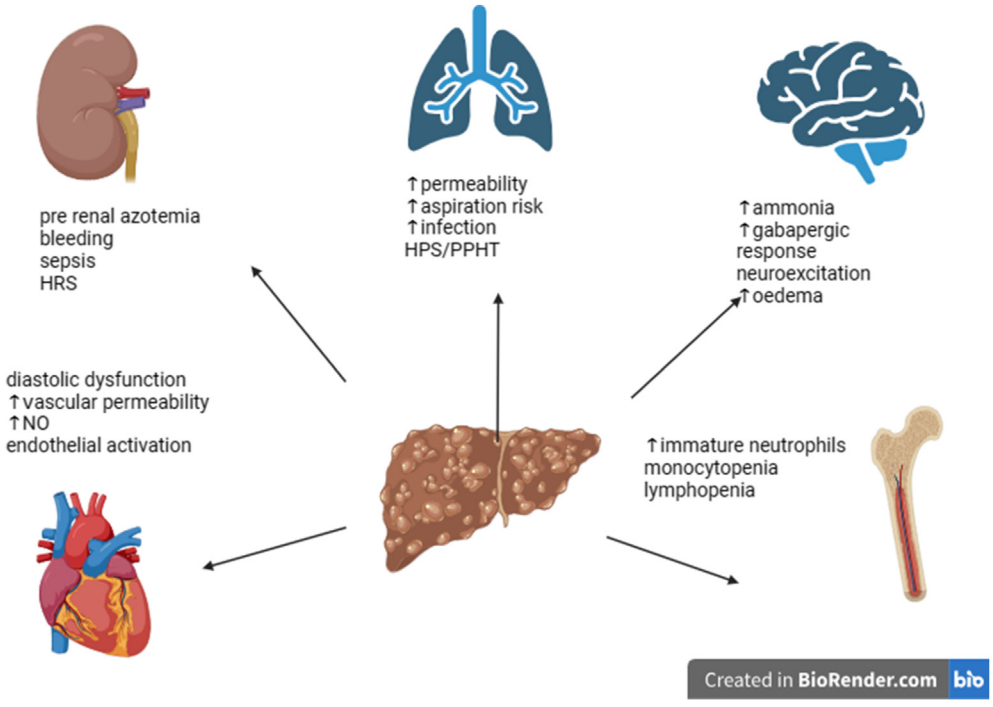

Figure 2. Extrahepatic organ failure in acute-on-chronic liver failure (ACLF). Multiple extrahepatic organs are affected in the inflammatory pathogenesis of ACLF. There is wide variation in those extrahepatic aspects where there is a known molecular mediator and those where considerable mechanistic uncertainty remains. Currently, the cardiac, respiratory, and renal failures at levels where advanced organ support is required represent the highest risk of mortality and where progression to transplantation may be complex.

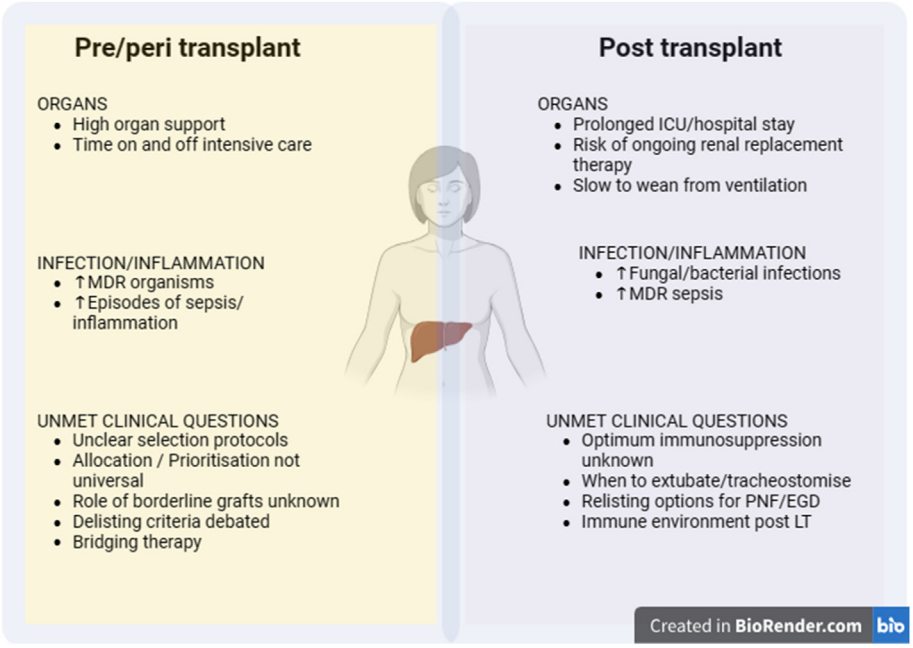

Figure 3. Pretransplant/peritransplant/posttransplant immune/inflammatory and clinical implications for patients undergoing liver transplantation for acute-on-chronic liver failure (ACLF). The infectious complications of ACLF carry over into the posttransplant period where repeated posttransplant infections from multidrug resistant organisms lengthen intensive care and hospital length of stay. There is less certainty on the immune landscape post-LT for ACLF and the role of the adaptive immune system under the influence of infection and pharmacologic immunosuppression requires urgent investigation.

vital areas. First, the definition of ACLF requires refinement. It is too broad to allow meaningful design of clinical trials unless prespecified ACLF subgroups are used, and this will be under the control of individual investigators without guidance from expert groups. The lack of a need for hyperbilirubinemia/coagulopathy (ie, true liver failure) means that some patients with cirrhosis and preserved liver function (but extrahepatic organ failure) can be brought under the same umbrella as a patient with alcoholic hepatitis and high-grade hepatic encephalopathy (HE). While we await this change, investigator should focus on subgroups such as alcohol, vasoplegic shock, and ACLF due to sepsis.

Even without this future homogeneity, it is not yet clear how this improved immunopathology understanding will lead to better outcomes. Several large clinical trials in plasma exchange, modification of the TLR9 axis, and checkpoint inhibition are ongoing, and we await their results with interest. In the interim, all patients with ACLF should be considered for transplantation or clinical trials unless there are compelling reasons against. The global liver community has made significant progress in understanding and treating this disease, and future work on expanding the role of transplantation and using novel therapies are hopeful of further improvements in survival for some of the sickest patient in liver clinical practice.

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Declaration of competing interest

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